Reflections of a lifetime in dermatopathology

Phillip H McKee

Abstract

During my lifetime, pathology has changed beyond recognition. From the early days of H/E-based diagnoses when the discipline really was an art form, there has been a step wise transformation through electron microscopy, immunofluorescence, immunohistochemistry and molecular studies to a much more scientifically based approach. Having said that, the need for clinicopathological correlation still remains the bedrock of our speciality. Training the next generation of dermatopathologists has been the greatest reward throughout my career.

Keywords clinicopathological correlation; McKee's pathology of the skin; social media

> "Where observation is concerned, chance favours only the prepared mind."
>
> Louis Pasteur 1854[1]

Throughout my career, I have been primarily a morphologist with a passion for clinicopathological correlation. I chose an academic setting not as a consequence of altruism but more because I have always enjoyed teaching. To be involved in training the next generation of dermatopathologists has been such a privilege. Both in the UK and the USA, I have been surrounded by Fellows in dermatopathology and it is so satisfying to have watched them spread their wings and fly off to all corners of the world to practice our specialty. I am so proud of them. From a career point of view, what could be better?

A successful career in dermatopathology requires expertise in both pathology and dermatology. I came up the hard way when there were no training programs available. Attendance at dermatology clinics and ward rounds gave me only a very superficial understanding of the subject. I had to make up for the rest from dermatology tomes and when possible going to see patients myself. The "Rook Book" was my fountain of knowledge.[2] The introduction of various qualifications in dermatopathology including Certification in Dermatopathology by The American Boards of Pathology and Dermatology and the Diploma in Dermatopathology granted by The Royal College of Pathologist's have greatly improved the situation. Professor Nick Wright and I were responsible for the establishment of the training program and examination for the latter qualification. In Europe, qualification is now through the Union Européenne Médecins Spésialistes (UEMS) International Board Certification in Dermatopathology (Diploma in Dermatopathology). Thus, a dermatopathologist can come from either pathology or dermatology backgrounds. In an ideal world, full time training in both Dermatology and Pathology before undertaking a Fellowship in Dermatopathology would be best but unfortunately, it would be too time consuming to be practicable.

Life is a complex series of decisions. Little does one appreciate their importance as an adolescent or young adult. Making one decision or another has such extraordinary ramifications. Change in just one variable has the consequence of an exponential change in the system.[3] It was thus never my original intention to study medicine, let alone pathology but parental influence determined that I would continue in the family tradition. Like other teenagers, I was thinking more along the lines of becoming a fireman, or a pilot or doing nothing very much at all. Having said that, the older generation knew best. And so, in 1965 at the age of 17 years and a bit, I embarked on training in the Medical School at Queen's University Belfast.

Fast forwarding to 1972, a game-changing year for me. I had completed my internship at the Royal Victoria Hospital Belfast, Northern Ireland and began training in pathology under the guidance of Professor D. L. Gardner. I clearly remember my first encounter with the autopsy room on day 1 of the program. A middle-aged male had somehow become caught up in the inner workings of a very large industrial canning machine. He had been disembowelled and partially dismembered. Such a horrifying introduction to the specialty! Needless to say, some of the residents fainted. I was very close to a career-change from that experience.

Although I found surgical pathology more to my liking, challenging wouldn't even begin to describe the Herculean task of grasping even the fundamentals. In those days, the subject was much more of an art than a science. To quote the late Bernie Ackerman, "diagnosis is all about pattern recognition". A melanoma is a melanoma because that's what a melanoma looks like! I can't imagine that there are any dermatopathologists who have not been enthralled by his magnum opus "Histologic Diagnosis of Inflammatory Skin Diseases: An Algorithmic Method Based on Pattern Analysis". He was certainly one of my earliest influences. Contrariwise, one of our Professors had the unshakable belief that "it is what it is because I say that it is". Difficult to argue with that but hardly a great educational experience. To us, as very junior residents, pathology was an unfathomable mystery. How on earth would one ever master this difficult subject? Obviously with the passage of time, we gained experience and came to think that we had a much better understanding of the subject than we really had. Little did we know! I am still learning. I learn something new every day. There is always someone who knows more than oneself. We like to think of a hierarchical system with the Professor knowing the most and the young resident knowing the least and yet at sign out, sometimes, it is the most junior who spots the mitosis in a nevoid melanoma or who has spent hours researching a particularly difficult case and come up with a diagnosis that none of the rest of us has ever heard of!

Histopathology in those days was based solely on hematoxylin and eosin-stained slides and very limited special stains. If one didn't recognize an entity with H/E then one was lost! Having said this, life was a great deal easier. So much had yet to be discovered. Immunofluorescence was in its infancy and

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generally not available. Immunohistochemistry and molecular studies hadn't yet been dreamed of. Inflammatory subepidermal blisters were either neutrophil-rich representing dermatitis herpetiformis or eosinophil-rich and diagnostic of bullous pemphigoid Nothing to it really! Our special stain armamentarium included Masson Fontana for melanin, DPAS, Alcan blue and mucicarmine for mucin and reticulin to outline tumor nodules. The Warthin Starry for spirochetes never worked! With hindsight, it is a wonder we ever got any diagnosis correct. The patients must have survived despite us.

On a weekly basis we were interrogated in front of the entire departmental staff for about an hour on 12 unknown and very difficult cases-the so-called "Red Box" meeting. Confidence was of utmost importance but bluffing never succeeded. Useful life lessons for the future. Dermatopathology slides figured prominently, largely because none of the senior staff like the subject and they always wanted a consensus diagnosis! The meeting was beyond stressful. A wrong diagnosis resulted in total public humiliation lasting until the following meeting and beyond. Tears sometimes followed. We therefore took these meetings very seriously indeed. They were an invaluable tool in preparing us for the day when we would have to take the responsibility of giving a definitive diagnosis ourselves. Training in those days was a lot more flexible than in today's litigation-driven environment. From the second year of the residency, we were given increasing responsibility for signing out the more straightforward cases on our own with periodic spot checks by members of the faculty. Our excitement knew no bounds when we were permitted to report appendices, gall bladders, cutaneous cysts, viral warts and the like unsupervised. In this way, our transition to a consultant position or member of faculty was not so abrupt as it is nowadays.

Sometime around midway through my second year I experienced an epiphany. It was completely serendipitous but nevertheless, it set the scene for the rest of my working life. I was walking along the corridor in the Pathology Department when I saw the Deputy Head of Department and a senior consultant in Dermatology having a heated discussion. My Professor called me over and announced, "Here he is, our expert in Dermatopathology, he will make sure that all of your cases are reported perfectly!". I was dumfounded and horror struck by this statement but in no position to argue and so armed with an early edition of Lever's "Histopathology of the Skin" and "Dermal Pathology "by Graham, Johnson and Helwig, I set about the daunting and seemingly impossible task of teaching myself dermatopathology.

One of my lasting memories from those early formative years was the case of an elderly farmer who presented with a tumor behind the ear surrounded by a large purple plaque (Figure 1). Biopsy revealed primary cutaneous angiosarcoma, the first case that I had seen. The patient died soon after admission and at autopsy had metastases in the liver, vertebrae and femur (Figures 2 and 3). Skin tumors were a lot more serious than I had believed. This formed the basis of my first publication.[4]

As part of my residency, I was obliged to undertake a Doctorate in Medicine (MD) research thesis. I had recently encountered a patient with Di George syndrome and it was decided that I would try to develop an animal model with absent parathyroid glands and thymus. Using a magnifying glass and

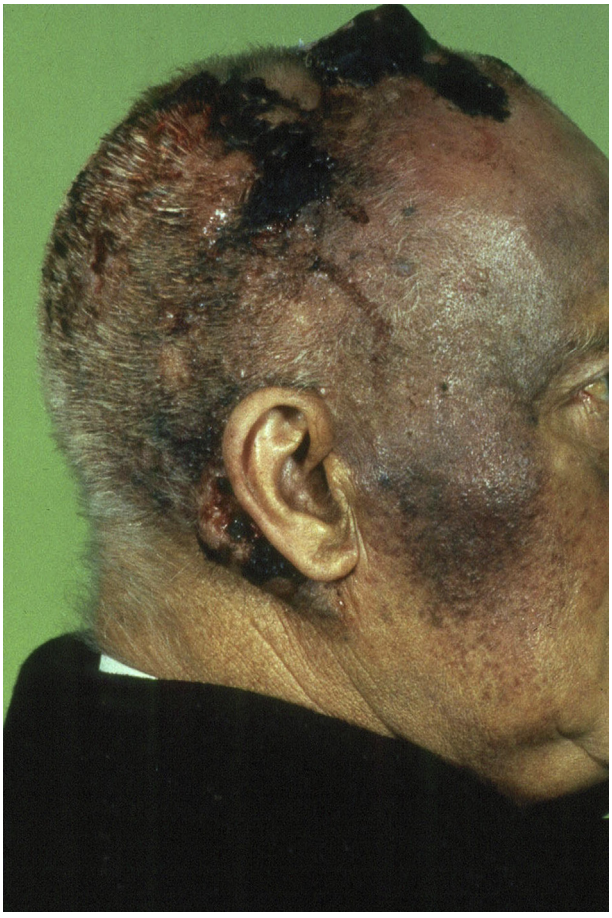

Figure 1 Cutaneous angiosarcoma: in addition to a tumor nodule behind the ear, there is purplish discolouration affecting the patient's face and scalp (the patient died in 1975).

very basic electrocautery equipment, I set about my task with great enthusiasm. A very large number of Wistar rats died at my hands before the Head of Department decided that "enough was enough" and my vivisection license was revoked. I was subsequently awarded my MD degree by the University of Medicine, Belfast in 1992.

As mentioned above, during my training, I started attending Dermatology clinics, ward rounds and the weekly conference. I presented the pathology at the last and slowly over the years gained experience in dermatopathology. Northern Ireland is a very small country and it wasn't difficult for me to become quite a large fish in the pond. However, in 1978 I decided that I had better get some proper training in the subject and Professor Edward Wilson—Jones at St. John's Hospital for Diseases of the Skin very kindly accepted me as a Fellow in Dermatopathology. At that time, St John's Hospital was a very curious and deceptive rhomboidal-shaped building with a very narrow front which opened up into a very substantial hospital building (Figure 4). I had an appointment to meet with the Professor before I took up my appointment. Young and care free, I thought that I had better dress for the occasion. At that time in the early 70's, denim was very much the fashion and so I arrived in a blue denim suit and shirt with a black knitted tie and highly polished pointed black leather shoes! Edward and the late Neil Smith were waiting at the

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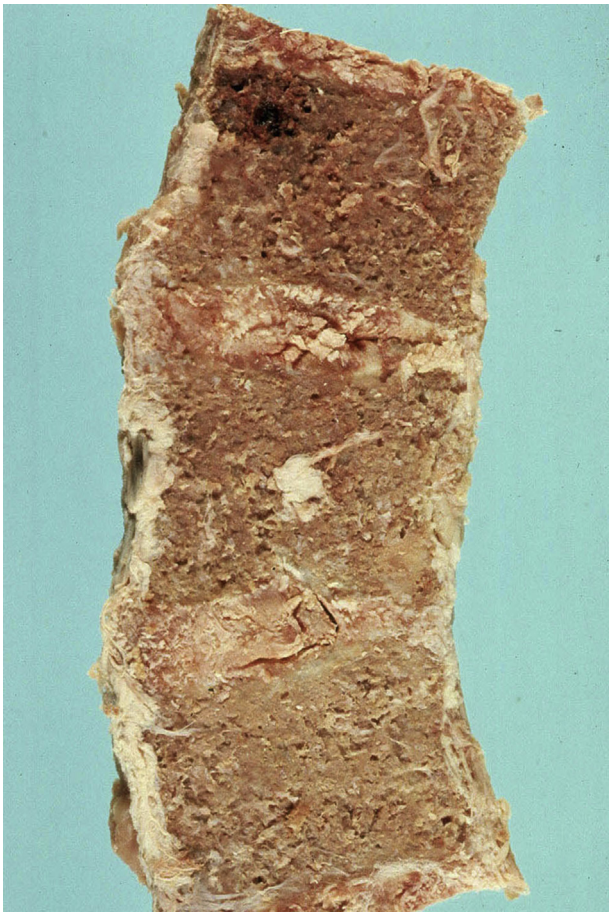

Figure 2 Cutaneous angiosarcoma: metastases in the vertebral column.

Figure 4 St John's Hospital for Diseases of the Skin: the original hospital was situated in Lisle Street near to Leicester Square, London.

top of the stairs in the entrance hall. Neil took one look at me and suggested that I had come to the wrong address. Perhaps I had meant to visit next door-one of Leicester Square's many brothels. St John's was sandwiched between two such premises. This was extremely handy for customers of the latter as they could visit the Venereal Clinic immediately after their assignation! Both Edward and Neil had a wicked sense of humor and I was at their mercy for quite many years.

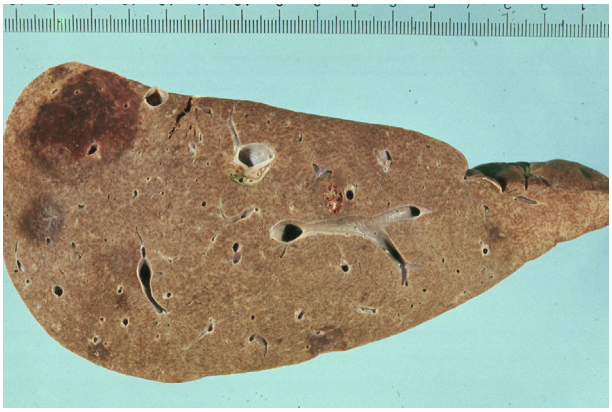

Figure 3 Cutaneous angiosarcoma: the liver contains multiple tumor nodules.

I remember my first day at St. John's with vivid clarity. I had just entered the reporting room and Professor Wilson–Jones, and the late Drs. Neil Smith and George Wells were looking at cases. Professor Wilson–Jones greeted me warmly and asked if I would like to give an opinion on a fascinating case-very easy really, hardly worth my while bothering with. My heart sank as I realized this was the moment when I sank or swam! I looked down the microscope and saw a large and very edematous vascular lesion (Figures 5 and 6). Without hesitation, I said "this is Orf". It was just a shot in the dark which happened to be correct. The day and my reputation were saved. I was never tested like this again!

Late in 1978 I was appointed consultant pathologist to St Thomas' Hospital and subsequently in 1992 to St John's Hospital for diseases of the Skin and The Institute of Dermatology (at that time incorporated into St Thomas' Hospital). These were wonderful years when I was able to immerse myself completely in dermatopathology surrounded by numerous like-minded people. St John's Hospital is a truly unique institution combining some of the very brightest of British dermatologists. I leant so much from them. I have some great memories from those days. One of those "once in a lifetime events" took place during sign-out one afternoon. Earlier that day I had read an article about a peculiar lesion that generally affected the oral cavity but which might exceptionally present in the skin, most

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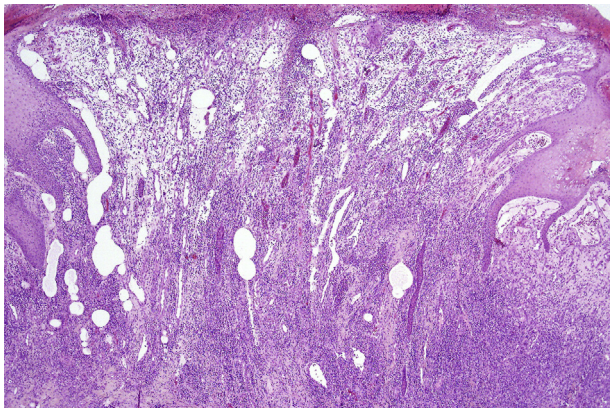

Figure 5 Orf: low power view showing an acutely inflamed, richly vascular and oedematous polypoid lesion (courtesy of Dr E. Calonje, The Institute of Dermatology, London).

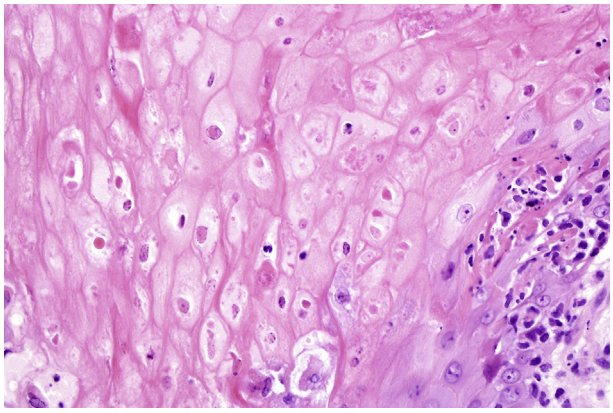

Figure 6 Orf: eosinophilic inclusions are present in the cytoplasm and occasional nuclei (courtesy of Dr E. Calonje, The Institute of Dermatology, London).

often in the genital region of females. This was verruciform xanthoma which as the name implies has a verrucous silhouette. Anyway, I turned up at the multi-headed microscope and the residents were very excited about the first case. They wouldn't give me any information. I glanced at the slide in the slide tray and said "this is a typical verruciform xanthoma and I was right" (Figures 7 and 8). Such an inspired guess. My reputation as a dermatopathologist who didn't need a microscope was made. I basked in this glory for as long as I could.

During those years, I developed a love for electron microscopy and immuno-electron microscopy of bullous dermatoses for both diagnostic and research activities. Deciding whether the split lay above or below the lamina densa and where the immunoreactants localized to was regular source of excitement (Figure 9). Partly as a consequence of my interest in blister formation, I became involved with the late Dr. Robin Eady and Professor John McGrath's work with epidermolysis bullosa patients. I served as the pathologist for all of their squamous cell carcinomas (Figures 10–12). However, the onset of the molecular era in pathology with various immunoblotting techniques soon supplanted morphology. The diagnosis and classification of epidermolysis bullosa became much firmer and was defined

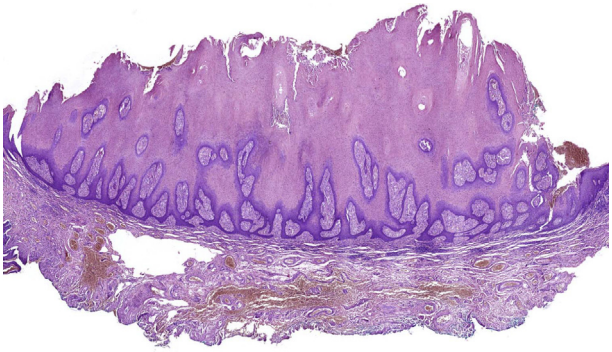

Figure 7 Verruciform xanthoma: scanning view showing massive hyperkeratosis, acanthosis and superficial acute inflammation (courtesy of Dr A. Kalmykova, CSD Health Care, Kyiv, Ukraine).

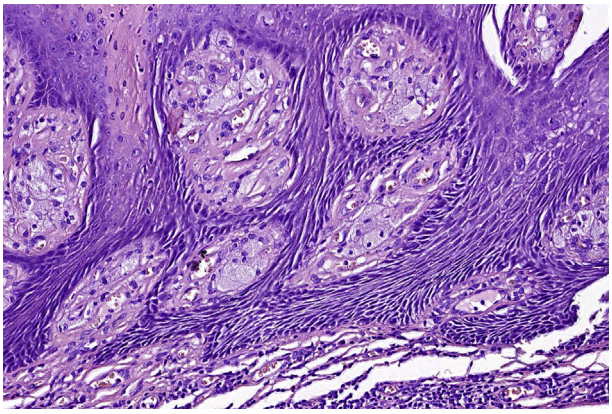

Figure 8 Verruciform xanthoma: xanthoma cells are present in the papillary dermis (courtesy of Dr A. Kalmykova, CSD Health Care, Kyiv, Ukraine).

by mutations in basement membrane genes rather than the constellation of clinical features with innumerable eponyms. It was enormously exciting that the antigens targeted in the subepidermal immunobullous dermatoses were the very same ones that were affected in the epidermolysis bullosa spectrum. Everything neat and tidy! With immunohistochemistry. It became possible to localize the level of separation either

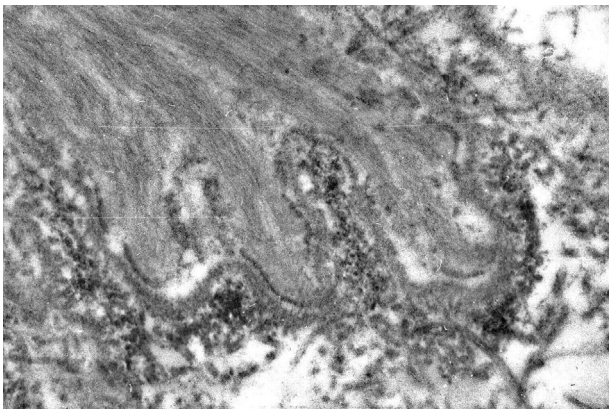

Figure 9 Epidermolysis bullosa acquisita: the immunoreactants are present below the lamina densa.

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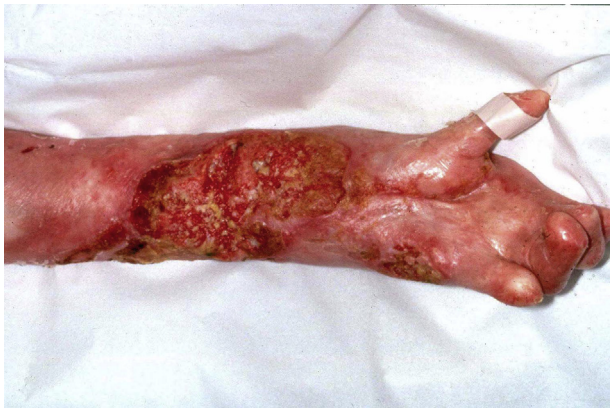

Figure 10 Recessive dystrophic epidermolysis bullosa: in addition to gross scarring and deformity, there is a large area of ulceration (courtesy of The Institute of Dermatology, London).

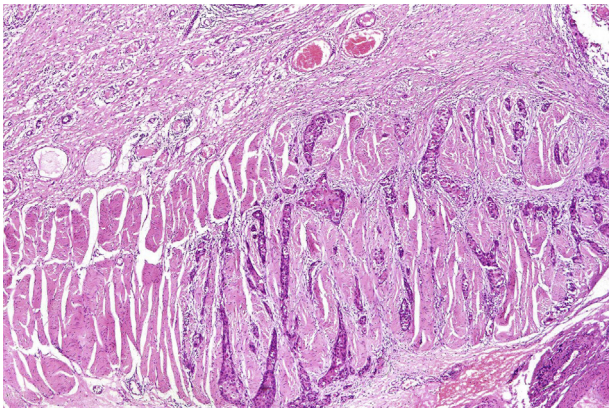

Figure 12 Recessive dystrophic epidermolysis bullosa: the tumour has extended deeply into a tendon.

through demonstration of deposits of immunoglobulin and complement along the floor or roof of a blister cavity or by identifying the location of the" basement membrane" using antibodies to type IV collagen or laminin. The use of split skin substrates in indirect studies was also a valuable tool for the morphologist. However it is rather humbling to remember that in many parts of the world, immunofluorescence is still not available and that diagnoses depend solely upon clinical judgement and H/E histopathology.

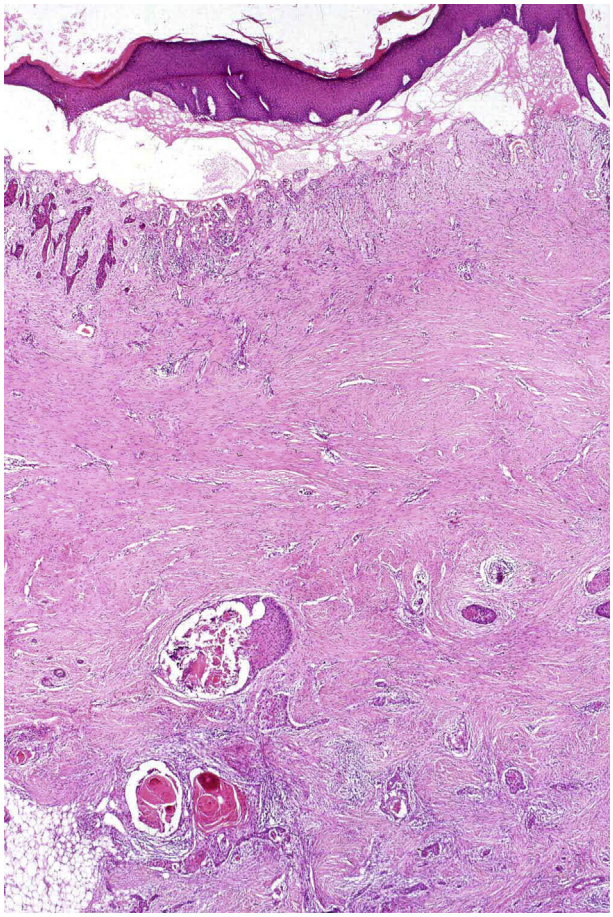

Figure 11 Recessive dystrophic epidermolysis bullosa: in addition to subepidermal blistering, there is a squamous cell carcinoma extending into the subcutaneous fat.

Histopathology and dermatopathology were transformed by the evolution of the era of immunohistochemistry. What powerful tools we acquired. Needless to say, there were disadvantages! Specificity was short-lived. If one didn't at least have a good idea about the possible diagnosis of a tumor, selecting which antibodies to use could be problematical. This sometimes led to a blunderbuss approach of using a whole range of antibodies in the hopes that something would stick. I remember many instances when a resident would say "this is a spindle cell tumor, I would use the following immunocytochemical battery". It used to infuriate me! Nevertheless, our simplistic disease and in particular tumor classifications were rapidly rendered obsolete. Diagnoses made with supreme confidence based on the hematoxylin and eosin-stained sections could be and were challenged by the new generation. As a consequence, the patients benefited enormously and therapies could be based on these much more precise diagnoses. So much has changed throughout this era. Classifying cutaneous lymphoma was a major problem. During my training in Pathology we initially used the Rappaport classification of lymphoma which was based on morphology. This was supplanted by the Lukes (1974) and Kiel Classifications (1975) which included morphology, immunological studies and tumor grade. Further improvements were the REAL, the EORTC and WHO classifications. The EORTC classification recommended was particularly important as it recommended that primary cutaneous lymphoma merited a classification in its own right based on clinical, histological and immunophenotypic observations. Today we use the 2018 update of the WHO-EORTC Classification which combines the best of both worlds using clinical, morphology, immunohistochemistry and molecular data. When I started my residency in pathology, cutaneous lymphoma and lymphoma-like conditions included mycosis fungoides, Sézary syndrome, pagetoid reticulosis, follicular mucinosis, actinic reticuloid, histiocytosis X, lymphocytoma cutis and benign lymphocytic infiltrate of Jessner-Kanof. The subject has changed beyond recognition. I think that nowadays, the subject is best dealt with by subspecialists dealing primarily with lymphoma.

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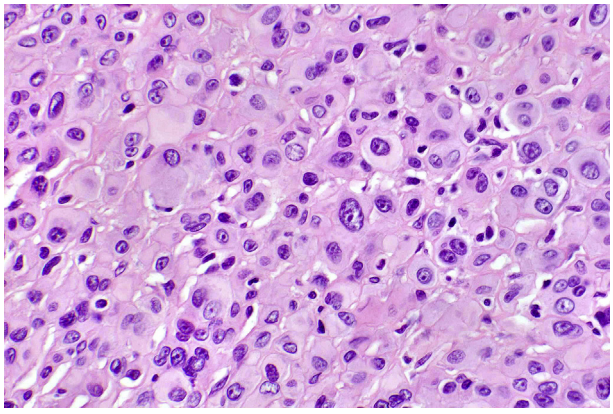

Figure 13 BAPoma: the tumor can be readily identified by the presence of pink, hyaline cytoplasm (courtesy of Dr C. Cerruto, Associates in Dermatology, Florida, USA).

"Pathology of the Skin with Clinical Correlations" was to dominate my life. It was in the mid 1980's that through a great friend of mine, Dr. Antony Du Vivier, I had the pleasure of meeting with Timothy Hailstone and Vitek Tracz, joint owners of Gower Medical Publishing. They wanted me to write a book on Dermatopathology. My excitement knew no bounds. Success! I was going to be an author. At that time Professor John Tighe was Head of Department of Pathology and when I told him my exciting news he responded "writing a book is about as much value to your curriculum vitae as doing a 6-week locum in an under developed country"! Well, my ego was damaged almost beyond repair. Never the less I set out to write the book despite his scathing comment. It is amazing how one brims with self-confidence and arrogance at such a young age, Without the bare minimum of references, I proceeded to write and illustrate "Pathology of the Skin with Clinical Correlations". To my surprise and relief, it was a great success and a 2nd edition was commissioned. I realized with each succeeding edition that the book needed to acquire greater respectability in the form of considerable extensive literature searches and ever-increasing numbers of references. Nowadays, people have PubMed online at their disposal and have no idea how tedious it was to search through the huge printed volumes that was our lot in life. The book became a huge undertaking and came to dominate my life and with as a result, with succeeding editions it became necessary to add editors and chapter authors to help manage it. I can remember when our vacations at our holiday home in France were spent reading innumerable articles and writing frantically rather than attending to my sun tan! I am particularly indebted to Eduardo Calonje, Thomas Brenn and Alex Lazar who made the fourth edition possible. Eduardo took on the role of senior editor in the 5th edition and what a fabulous job he has done. I almost have to pinch myself to believe how such a modest beginning has turned into a magnificent tour de force. I am so grateful to all of my friends who have contributed to the book.

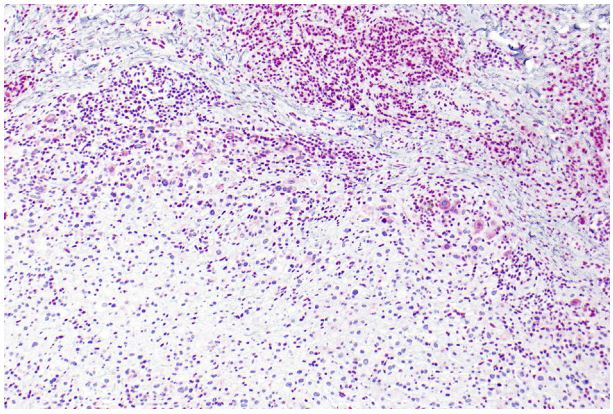

Figure 14 BAPoma: there is loss of BAP1 expression in the tumor cell nuclei whereas it is evident in the associated banal nevus cells (courtesy of Dr C. Cerruto, Associates in Dermatology, Florida, USA).

In 1998, through the efforts of Professors Ramzi Cotran and Christopher Fletcher, I crossed the pond to become Director (Chief) of Dermatopathology at Brigham and Women's Hospital and Harvard Medical School.

Melanocytic pathology comprised the majority of my diagnostic workload. It is fraught with hidden and not so hidden dangers. The potential for litigation has made the problem considerably worse resulting in the practice of "defensive medicine".[5] This has resulted in the commonly recommended re-excisions that bedevil daily practice. These are time and resource consuming and of doubtful benefit to the majority of patients. Similarly, the use of immunohistochemistry for difficult melanocytic cases has sky-rocketed. This has been partly a result of lack of confidence and yet the overwhelming percentage of cases can be readily diagnosed on the basis of the hematoxylin and eosin-stained sections. While in Brigham and Women's Hospital, dysplastic nevi dominated my life. I cannot imagine that Clarke and Lynch could ever have anticipated that the term would have resulted in a firestorm of controversy that reverberates even to this day.[6,7] The Barnhill grading system proved to be even more contentious.[8] In the Boston environment, dysplastic nevi were considered very real and grading was of the utmost importance. In fact, if I forgot to give the lesion a grade, I sometimes received a call from an irate dermatologist complaining that without a grade he/she didn't' know whether to re-excise the nevus or not.

Spitz nevi were also a challenge. Following Sophie Spitz's seminal paper in 1948, the realization that lesions that had been previously diagnosed as melanoma in children and adolescents were in fact benign lesions was a seminal moment in melanocytic pathology.[9] Although she used the term "benign juvenile melanoma" this was soon replaced with Spitz nevus. I remember well being taught that these pleomorphic lesions were all Spitz nevi and therefore of no biological consequence. This happy state of affairs lasted until 1989 when Dr. KJ Smith and co-workers described a series of 32 lesions diagnosed as malignant spindle cell and epithelioid cell nevi with atypia and metastasis (malignant Spitz nevus).[10] Six of these patients had lymph node resection and all contained metastatic tumor. The limited follow-up disclosed that all patients were alive and well. I contacted Dr. Smith some years after this paper was published to see if there was any further follow-up information but unfortunately this was not possible. This publication planted the seeds of doubt. At the same time, either through personal experience or from the literature, we became aware that occasional "malignant Spitz nevi (Spitzoid melanoma) with fatal outcome could be encountered.[11] Risk assessment grading

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systems were proposed categorising lesions into low-, medium- and high-risk categories.[12] In addition a plethora of terminologies were proposed to try to identify which Spitz lesions should be treated with caution including atypical Spitz nevus, atypical Spitz tumor and Spitz tumor of uncertain malignant potential.[13],[14] The problem became much worse with the introduction of the shave biopsy procedure. Pathologists were faced with the impossible task of deciding upon the likely biological potential of a Spitzoid lesion with only half of the tissue available for study! This resulted in a great diminution in the number of cases in which a frank diagnosis of Spitz nevus was made. An ever-increasing number of atypical Spitz nevi being reported. There are a few lessons to be learnt from this sad state of affairs. Firstly, the clinicians should not shave problematical nevi in the first place. If a lesion is sufficiently worrying to need histological study, then the whole of the lesion should be made available to the pathologist. This is just common sense. From the pathologist's point of view, it should be remembered that malignant Spitz nevus (Spitzoid melanoma) in young people is vanishingly rare and thus with any given Spitzoid lesion a presumption of benignancy should be made initially until a really good cause is found to render a diagnosis of melanoma. Recently, histological features that are thought to be associated with a more likely malignant potential including presence of mitoses, mitoses near the base of the lesion and an inflammatory reaction have been published.[12] Immunohistochemistry has proven to be of some help. S100 protein can be valuable in demonstrating more clearly the presence of maturation with depth. Low expression of Ki67 and Cyclin D1 favor Spitz nevus as does the absence of p53 staining. More recently determination of p16 nuclear expression has proven to be very valuable[15] Retention favors a Spitz nevus whereas loss is a feature of melanoma. Various algorithms to help with this diagnostic dilemma combining immunohistochemistry, fluorescence in situ hybridization and comparative genomic hybridization have been proposed.[15] Most recently molecular evaluation has been added to our diagnostic armamentarium.[16],[17] There is some light at the end of the tunnel. The identification of mutations in the BAP1 and ALK genes have enabled us to identify particular entities previously classified most often in the atypical Spitz nevus category (Figures 13 and 14).[18]

This brings me to the present. People often quote the aphorism "you only get out of life what you put in". I think that this is only half of the truth. To my mind, the rewards are far greater than the sacrifices. Dermatopathology has certainly been my life over the past decades, but I have gained much more than I put in. There are so many rewards that have no monetary value. I think trust from the patients and the clinicians is the greatest gift. As physicians, we owe it to our patients to give 100% of ourselves. I used to teach residents that even a boring epidermoid cyst is of importance to the patient. My rule of thumb when looking at cases was to pretend that the specimen came from a family member or close friend.

After moving to Arizona in 2004, in addition to completing a number of books. I developed a consultation practice and gently dipped my toes into the social media world. I was initially involved in the web site Dermpath Pro established by Dr. Iskandar Chaudry and later took part in Dermpedia, Professor Artur Zembowicz's brainchild. This was such an extraordinary time for me. To be able to teach residents and fellows through these platforms was beyond anything that I could have dreamed of.

In 2017, following the advice of Professor Jerad Gardner, I resolved to embark on a totally new venture. I decided to create a Facebook group (McKee Derm) where dermatologists and dermatopathologists could come together in a safe environment and share interesting or problematical cases. It would be a way that I could give back to the community that had been so kind to me. Teaching residents and fellow was my first intention but the Group developed a life of its own and like Topsy, it grew and grew. Currently there are over 14,000 members. There are now experts in all of the subspecialties in dermatopathology. Each month we have 300–400 cases posted. With the interest generated by the many comments, although the Group in no way attempts to replace formal consultations, often the diagnosis becomes obvious.

We live in such exciting times. Nothing stays still for very long. I can't imagine what the future holds for today's young pathologists.

For the younger folk reading this article, Horace could not have said it better:

> While we're talking, time will have meanly run on: pick today's fruits, not relying on the future in the slightest.
>
> Odes (23 bc)

I would like to take this opportunity to thank my wife and very best friend Gracie without whose support most of the above would never have happened and also to thank the many residents and fellows whom I have taught. Many of these have become close friends including Eduardo Calonje, Chris Fletcher, Thomas Brenn, SH Tan, Brigid Maguire, the late Neera Patel, Deidre Maguire, Susan Szakacs-Vittay, Wayne Grayson, Alex Lazar, Artur Zembowicz, Vince Liu, Marcela Lima Saeb, Kelly Culpepper, and Marcus Bosenberg to name but a few. McKee Derm would never have become the success that it is without the supprt of Jerad Gardner, Antonina Kalmykova, Adrienne Jordan and the other adminstrators. ◆

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